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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,642	01/28/2004	Anthony Atala	105447-2	4621

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NUTTER MCCLENNEN & FISH LLP
WORLD TRADE CENTER WEST
155 SEAPORT BOULEVARD
BOSTON, MA 02210-2604

EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
09/02/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@nutter.com

Office Action Summary	Application No.	Applicant(s)	
	10/766,642	ATALA ET AL.	
	Examiner	Art Unit	
	ALLISON M. FORD	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-10,12,23-26,28,29 and 33-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-10,12,23-26,28,29 and 33-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the appeal brief filed on 5/26/2009, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Terry A. McKelvey/

Supervisory Patent Examiner, Art Unit 1655.

Response to Arguments/Amendments

Applicants' arguments submitted on 5/26/2009, as part of the appeal brief, have been fully considered.

Applicants have traversed the rejection under 35 USC 103(a) on the grounds that none of the cited references, alone or in combination, teach all of the features of the method of the instant claims.

Applicant notes the differences between each reference and the method of the instant claims. Applicants further assert there is no suggestion that the primary reference, Naughton et al, is unsatisfactory, and the Examiner has not articulated a clear rationale supporting why the method of Naughton et al would be modified. Applicants further assert the Examiner has improperly relied on impermissible hindsight. Applicants further assert the number of references required to reconstruct the claimed invention is indicative of non-obviousness.

In response to Applicants' argument that none of the cited references, alone or in combination, teach all of the features of the methods of the instant claims, it is respectfully submitted that the rejections have been re-written to more clearly address each of the limitations of the instant claims. Applicants have not particularly pointed out any specific deficiency in the grounds of rejection, or limitation which they feel is not clearly taught or suggested by the cited references. Therefore the argument is found unpersuasive.

In response to Applicants' argument that one would not have been motivated to modify the method of Naughton et al, because no deficiency was noted in the method of Naughton et al, it is respectfully submitted that such a requirement (recognition of a deficiency in the art and an explicit motivation to modify or combine prior art teachings) is not the standard for a proper rejection under 35 USC 103(a). In the Supreme Court decision in *KSR International Co v Teleflex Inc* the court stated, "Rigid application of "teaching, suggestion, or motivation" test, under which patent claim is proved obvious only if prior art, nature of problem addressed by inventor, or knowledge of person having ordinary skill in art reveals some motivation or suggestion to combine prior art teachings, is inconsistent with expansive and flexible "functional approach" to resolution of obviousness issue, under which scope and content of prior art are determined, differences between prior art and claims at issue are ascertained,

level of ordinary skill in pertinent art is resolved, and secondary considerations such as commercial success, long felt but unsolved needs, and failure of others may be considered if doing so would prove instructive; rigid TSM approach is therefore rejected." See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) at page 1386 (emphasis added). However, the rejection of record has been modified to clearly show that one of ordinary skill in the art would have been motivated to modify the method of Naughton et al, even though no deficiency was explicitly noted, to further involve administration of encapsulated cells engineered to transiently express an angiogenesis modulating agent because the angiogenesis modulating agent expressed by the encapsulated cells promotes cell survival and angiogenesis, and the goal of Naughton et al is to promote tissue assimilation and angiogenesis at the implantation site. Clearly the encapsulated cells would be expected to add to and improve the method of Naughton et al to achieve an enhanced therapeutic result.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991). However, to clarify and simplify the prosecution, the rejection has been split up into several

rejections, each rejection relying only on those references required to construct the rejection against the specific claims at hand.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6-8, 10, 12, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (US 2003/0007954), in view of Lu et al (Circulation, 2001) and Atala (US Patent 6,479,064), and further in view of Springer et al (J Gene Med, 2000), Rinsch et al (Gene Therapy, 20001) and Penn et al (US 2004/0161412 A1, as fully supported by provisional applications 60/405274 & 60/424065).

Naughton et al disclose a method for treatment of ischemic tissue, particularly ischemic myocardial tissue, comprising producing a three-dimensional stromal tissue construct and implanting the construct to promote vascularization of the ischemic region and regeneration of the damaged cells (See Naughton et al, Pg. 2, paragraph 0028). Specifically, the method of Naughton et al comprises:

(i) formation of a three-dimensional stromal tissue construct by inoculating stromal cells onto a three-dimensional scaffold; and then

(ii) implantation of the three-dimensional tissue construct at various ischemic regions of the heart, so as to allow assimilation of the stromal cells into the natural cardiac tissue (See Naughton et al, Pg. 5, paragraphs 0055-0057).

The three-dimensional scaffold may be formed of polymeric material, such as PGA, polylactic acid or collagen (See Naughton et al, Pg. 2, paragraph 0032).

The method of Naughton et al reads on a method of organ augmentation comprising selecting a population of cells to be assimilated at a target tissue region, culturing the cells on a polymeric matrix to produce an organ construct (specifically a stromal tissue construct) and implanting the organ construct at the target tissue region, thereby inducing assimilation of the cells of the construct into the ischemic region and augmenting cardiac function. (relevant to claims 1 and 8).

Regarding the types of cells cultured on the three-dimensional scaffold: Naughton et al teach the stromal cell populations can comprise fibroblasts as well as tissue specific cells, such as heart cells, particularly cardiac muscle cells and aortic smooth muscle cells (See Naughton et al, Pg. 3, paragraph 0034 & claims 3 and 4). Additional cells can be added to form the three-dimensional tissue, including endothelial cells (See Naughton et al, Pg. 3, paragraph 0038).

Naughton et al does not specify *myoblasts* as a species of cardiac muscle cells, nor *vascular* endothelial cells as a species of endothelial cells which may be cultured on the three-dimensional scaffold. However, it is submitted that inclusion of myoblasts as the particular species of cardiac muscle cells, and vascular endothelial cells as the particular species of endothelial cells would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

With regards to myoblasts: Lu et al teaches myoblasts are commonly used in formation of bioartificial muscle (See Lu et al, Pg. 595, col. 1). Because the tissue graft of Naughton is intended to augment the function of cardiac muscle, one would have thus been motivated to select myoblasts as the species of cardiac muscle cells to seed onto the construct of Naughton. One would have had a reasonable expectation of successfully using myoblasts as the species of cardiac muscle cell seeded onto the construct of Naughton because Lu et al teaches how to isolate myoblasts, and teaches myoblasts can

successfully be seeded onto scaffolds for formation of bioartificial tissues. Myoblasts are considered undifferentiated cells. (relevant to claims 1 and 6)

With regards to vascular endothelial cells: Vascular endothelial cells were routinely used in tissue engineered constructs to promote formation of a primitive vascular system (See Atala, col. 2, ln 19-52). Because one of the goals of the tissue construct of Naughton et al is to promote vascularization in the tissue construct, one would have been motivated to select vascular endothelial cells as the species of endothelial cells in the stromal tissue construct of Naughton in order to promote such vasculogenesis (See Naughton et al, Pg. 1, paragraph 0007). (relevant to claim 7)

Thus, in total, Naughton et al renders obvious a method of augmenting heart function in an ischemic patient, comprising selecting a population of cells to be assimilated at the ischemic cardiac tissue region, culturing the cells on a matrix to produce a stromal tissue construct, and implanting the stromal tissue construct at the ischemic region(s), thereby inducing assimilation of the cells of the construct into the ischemic region and augmenting cardiac function. The matrix may comprise a polymer scaffold, including a collagen scaffold. The cells seeded on the scaffold may comprise myoblasts and/or vascular endothelial cells. (relevant to claims 1 and 6-8).

Naughton et al does not teach or suggest a further step of implanting encapsulated cells which have been genetically engineered to express an angiogenesis modulating agent along with the three-dimensional tissue engineered stromal tissue.

However, implantation of encapsulated cells which have been genetically engineered to express angiogenesis modulating agents, such as VEGF or FGF-2, at sites in need of revascularization and/or angiogenesis were known in the art. The angiogenesis modulating agents expressed by the encapsulated

cells promote cell survival and vascularization at the implantation site. Springer et al and Rinsch et al are cited in support:

Springer et al discloses a method wherein myoblasts, transfected to express VEGF, are encapsulated in alginate-PLL microcapsules and then injected either subcutaneously or into the peritoneal cavity to promote blood vessel formation (See Springer et al, Pg. 280, col. 2). Springer et al report that, unlike non-encapsulated cells (their previous work) the encapsulated cells led to blood vessel formation and recruitment of endothelial and smooth muscle cells (See Springer et al, pg. 286, col. 2 – Pg. 287, col. 1).

Rinsch et al disclose a method for promoting revascularization and healing of ischemic skin tissue. The method involves implanting encapsulated, genetically engineered myoblasts, wherein the myoblasts were transfected with VEGF or FGF-2 (See Rinsch et al, Pg. 524, col. 1), under the ischemic zone at the time of implantation of a transplanted skin flap. In tissues wherein cells expressing FGF-2 were implanted, Rinsch et al report decreased necrosis (See Rinsch et al, Pg. 526, Table 2). Rinsch et al report formation of blood vessels around the implanted capsules (see Rinsch et al, pg. 526, col. 2).

Therefore, the teachings of Springer et al and Rinsch et al demonstrate that implanted encapsulated cells, such as myoblasts, engineered to express angiogenesis modulating agents VEGF and/or FGF-2, secrete the angiogenesis modulating agents external to the microcapsule effecting angiogenesis at the implantation site. Myoblasts are undifferentiated cells. (relevant to claims 1, 3 and 12, 34 and 35).

However, while both Springer et al and Rinsch et al report increased recruitment of endothelial cells and muscle cells and neo-blood vessel formation, both Springer et al and Rinsch et al also note that constituent expression of the angiogenesis modulating genes can produce deleterious results, so they suggest using transfection methods whereby the gene expression can be controlled (See Springer et al, Pg. 287, col. 1-2) or halting treatment after revascularization (See Rinsch et al, Pg. 524, col. 1). Following

Springer et al's suggestion, it would have been obvious to one of ordinary skill in the art to use myoblasts which will transiently express the angiogenesis modulating gene(s); such methods were known in the art, see Penn et al.

Penn et al teach transfecting a population of skeletal myoblasts with a VEGF expression vector by plasmid DNA transfection (See Penn et al, Pg. 7, paragraph 0092). Penn et al also teach that the VEGF can be transiently expressed for any suitable and defined length of time (See Pg. 8, paragraph 0100-0102). Penn et al teach that local and transient expression of VEGF is sufficient to induce neovascularization and minimize systemic effects and hemangioma formation (See Penn et al, Pg. 1, paragraph 0004). With regards to the length of time the VEGF is produced, Penn et al teach that the duration of the transient expression is a result effective variable that would be routinely optimized by one of ordinary skill in the art (See Penn et al, pg. 8, paragraphs 0099-0102). Penn et al teach that the cells can be transiently transfected so as to express a therapeutic amount of VEGF; Penn et al further teaches that it is well within the scope of one skilled in the art to determine the appropriate therapeutic amount on an individual basis, as factors such as size, age, sex, presence of other drugs, and concentration of the active drug, all effect the optimal duration of expression. Therefore, the duration of the transient expression of VEGF would have been routinely optimized by one of ordinary skill in the art at the time the invention was made, especially with lack of evidence to the contrary, submitting the claimed time period is critical. Penn et al further add that their cells, which transiently express VEGF, are useful to stimulate cell differentiation and regenerate ischemia damaged tissue (See Penn et al, Pg. 2, paragraph 0020 & Pg. 3, paragraphs 0044-0045). Therefore, at the time the invention was made, the benefits of transiently transfected cells, compared to constitutively transfected cells, was recognized in the art, and methods for producing such transiently transfected cells were known. Thus, in order to provide optimal and controlled delivery of the angiogenesis modulating agents, it would have been obvious to the artisan

of ordinary skill to encapsulate transiently transfected cells in the methods of Springer et al and/or Rinsch et al. (relevant to claims 1, 2 and 10).

Because the method of Naughton et al is intended to promote assimilation of the implanted tissue construct into the implantation tissue site, and to promote angiogenesis of the implanted tissue construct, as well as the ischemic tissue regions, and because the microencapsulated myoblasts of Springer et al and Rinsch et al are capable of promoting cell survival and angiogenesis, it is submitted that one of ordinary skill in the art would been motivated to co-implant the microencapsulated myoblasts of Springer et al and Rinsch et al, modified per the suggested method of Penn et al, for the purpose of enhancing cell survival and assimilation of the tissue construct of Naughton et al into the ischemic tissue site and to promote angiogenesis in and around the ischemic tissue site. One would have had a reasonable expectation of successfully co-implanting the encapsulated cells of Springer et al and/or Rinsch et al, modified to only transiently express the angiogenesis modulating agents, with the stromal tissue construct of Naughton et al because both Springer et al and Rinsch et al demonstrate that the microencapsulated cells can successfully be co-implanted at a target tissue site along with non-encapsulated cells, and the encapsulated cells do exert the predictable effect of enhancing cell survival and angiogenesis.

Thus, the cited references are considered to suggest a method of organ augmentation, specifically augmentation of the function of ischemic heart tissue, comprising: transiently transfecting a first population of cells (myoblasts) with a plasmid encoding the angiogenesis modulating agent VEGF, such that the myoblasts express the VEGF for less than about 3 weeks; encapsulating the transfected myoblasts (per the methods of Springer et al, Rinsch et al, and Penn et al); selecting a second population of cells, comprising myoblasts and vascular endothelial cells to be assimilated at the ischemic tissue region; culturing the second population of cells on an injectable polymer matrix to form a stromal tissue construct (per the method of Naughton et al); and co-implanting both the stromal tissue construct and the

encapsulated myoblasts at the target ischemic region of the heart, thereby inducing assimilation and differentiation of the myoblasts and vascular endothelial cells into the ischemic tissue region, augmenting cardiac function.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-3, 6-10, 12, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (US 2003/0007954), in view of Lu et al (Circulation, 2001), Atala (US Patent 6,479,064) and MacLaughlin et al (US Patent 6,692,738), and further in view of Springer et al (J Gene Med, 2000), Rinsch et al (Gene Therapy, 20001) and Penn et al (US 2004/0161412 A1, as fully supported by provisional applications 60/405274 & 60/424065).

The teachings of Naughton et al, Lu et al, Atala, Springer et al, Rinsch et al and Penn et al have been set forth above. The combined teachings are considered to render obvious the method of claims 1, 2, 3, 6, 10, 12, 34 and 35.

The combination of references differs from current claim 9 in that, while Naughton et al suggest use of collagen as the scaffold material (See Naughton et al, Pg. 2, paragraph 0032), Naughton et al does not specify collagen *type I* as the scaffold material.

However, at the time the invention was made a variety of materials were recognized as suitable scaffolding materials for formation of engineered tissue constructs. Specifically, MacLaughlin et al disclose formation of tissue constructs using one of microfabricated scaffolds, fibrous scaffolds, or hydrogel matrices (See MacLaughlin et al, abstract). The fibrous scaffolds are identical to those disclosed by Naughton, being formed of polymers, such as polyglycolic acid and/or polylactic acid (See MacLaughlin et al, col. 13, ln 3-30). Collagen, including collagen type I, may be part of the scaffold (See MacLaughlin et al, col. 13, ln 31-40).

Therefore, because Naughton et al and MacLaughlin et al both disclose scaffold materials which are appropriate for formation of engineered tissue constructs, it would have been *prima facie* obvious to one of ordinary skill in the art to substitute any of the scaffold materials for another, for the predictable result of successfully supporting growth of cells thereupon for formation of an engineered tissue construct which may subsequently be implanted at a target site. Substitution of one element for another known in the field is considered to be obvious, absent a showing that the result of the substitution yields more than predictable results. See *KSR International Co. v Teleflex Inc* 82 USPQ2d 1385 (US 2007) at page 1395. Therefore, substitution of collagen type I (disclosed by MacLaughlin et al), for the collagen scaffolding in the method of Naughton et al would have been *prima facie* obvious at the time the invention was made. (relevant to claim 9)

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-4, 6-8, 10, 12, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (US 2003/0007954), in view of Lu et al (Circulation, 2001) and Atala (US Patent 6,479,064), and further in view of Springer et al (J Gene Med, 2000), Rinsch et al (Gene Therapy, 20001) and Penn et al (US 2004/0161412 A1, as fully supported by provisional applications 60/405274 & 60/424065).

The teachings of Naughton et al, Lu et al, Atala, Springer et al, Rinsch et al and Penn et al have been set forth above. The combined teachings are considered to render obvious the method of claims 1, 2, 3, 6, 10, 12, 34 and 35.

The combination of references differs from current claim 4 in that, while Rinsch et al and Springer et al disclose encapsulation of *myoblasts* genetically engineered to express an angiogenesis

modulating agent, none of the cited references teach or suggest encapsulation of any other cell type which may be genetically engineered to express the same angiogenesis modulating agent.

However, at the time the invention was made, it was well within the technical skill level of the ordinary artisan to genetically engineer almost any cell type to express or overexpress a desired gene product, including genetically engineering vascular endothelial cells to express VEGF. Specifically, Naughton et al discloses engineering endothelial cells to express VEGF (See Naughton et al, Pg. 5, paragraphs 0047-0050). It is further submitted that it was within the technical skill level of the ordinary artisan to encapsulate any mammalian cell type in a manner equivalent to that disclosed by Springer et al and/or Rinsch et al.

Therefore, because each of Springer et al, Rinsch et al and Naughton et al disclose means for genetically engineering cells to express an angiogenesis modulating agent, it is submitted that it would have been *prima facie* obvious to one of ordinary skill in the art to substitute vascular endothelial cells for myoblasts as the cell type which is to be encapsulated and implanted as the source of the angiogenesis modulating agent, for the predictable result of expression of the angiogenesis modulating agent at the site of implantation.

Furthermore, the methods of Penn et al, regarding controlling the duration of the VEGF expression in the genetically engineered cells, would have been similarly applied to the encapsulated vascular endothelial cells, for the same predictable results of controlling VEGF expression and effect on the target tissue site.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 23, 26, 28-29 and 33-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (US 2003/0007954), in view of Springer et al (J Gene Med, 2000), Rinsch et al (Gene Therapy, 20001) and Penn et al (US 2004/0161412 A1, as fully supported by provisional applications 60/405274 & 60/424065).

Naughton et al disclose a method for treatment of ischemic tissue, particularly ischemic myocardial tissue, comprising producing a three-dimensional stromal tissue construct and implanting the construct to promote vascularization of the ischemic region and regeneration of the damaged cells (See Naughton et al, Pg. 2, paragraph 0028). Specifically, the method of Naughton et al comprises:

(i) formation of a three-dimensional stromal tissue construct by inoculating stromal cells, including fibroblasts, onto a three-dimensional scaffold; and then

(ii) implantation of the three-dimensional tissue construct at various ischemic regions of the heart, so as to allow assimilation of the stromal cells into the natural cardiac tissue (See Naughton et al, Pg. 5, paragraphs 0055-0057).

The three-dimensional scaffold may be formed of polymeric material, such as PGA, polylactic acid (See Naughton et al, Pg. 2, paragraph 0032).

Thus method of Naughton et al reads on a method of organ augmentation comprising selecting a population of fibroblasts to be assimilated at a target tissue region, culturing the fibroblasts on a polymer matrix to produce an organ construct (specifically a stromal tissue construct) and implanting the organ construct at the target tissue region, thereby inducing assimilation of the fibroblasts of the construct into the ischemic region and augmenting cardiac function. (relevant to claims 23, 36).

Though Naughton et al only report implanting the stromal tissue construct at a single site, it is submitted that it would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to implant multiple stromal tissue constructs at multiple ischemic sites, as needed, to

correct ischemic damage. One would be motivated to produce and implant as many tissue constructs as needed to correct all areas of ischemic damage in order to fully treat a patient. (relevant to claim 33)

Naughton et al does not teach or suggest a further step of implanting encapsulated cells which have been genetically engineered to express an angiogenesis modulating agent along with the three-dimensional tissue engineered stromal tissue.

However, implantation of encapsulated cells which have been genetically engineered to express angiogenesis modulating agents, such as VEGF or FGF-2, at sites in need of revascularization and/or angiogenesis were known in the art. The angiogenesis modulating agents expressed by the encapsulated cells promote cell survival and vascularization at the implantation site. Springer et al and Rinsch et al are cited in support:

Springer et al discloses a method wherein myoblasts, transfected to express VEGF, are encapsulated in alginate-PLL microcapsules and then injected either subcutaneously or into the peritoneal cavity to promote blood vessel formation (See Springer et al, Pg. 280, col. 2). Springer et al report that, unlike non-encapsulated cells (their previous work) the encapsulated cells led to blood vessel formation and recruitment of endothelial and smooth muscle cells (See Springer et al, pg. 286, col. 2 – Pg. 287, col. 1).

Rinsch et al disclose a method for promoting revascularization and healing of ischemic skin tissue. The method involves implanting encapsulated, genetically engineered myoblasts, wherein the myoblasts were transfected with VEGF or FGF-2 (See Rinsch et al, Pg. 524, col. 1), under the ischemic zone at the time of implantation of a transplanted skin flap. In tissues wherein cells expressing FGF-2 were implanted, Rinsch et al report decreased necrosis (See Rinsch et al, Pg. 526, Table 2). Rinsch et al report formation of blood vessels around the implanted capsules (see Rinsch et al, pg. 526, col. 2).

Therefore, the teachings of Springer et al and Rinsch et al demonstrate that implanted encapsulated cells, such as myoblasts, engineered to express angiogenesis modulating agents VEGF and/or FGF-2, secrete the angiogenesis modulating agents external to the microcapsule effecting angiogenesis at the implantation site. (relevant to claims 23, 28, 29, 36 and 37).

However, while both Springer et al and Rinsch et al report increased recruitment of endothelial cells and muscle cells and neo-blood vessel formation, both Springer et al and Rinsch et al also note that constituent expression of the angiogenesis modulating genes can produce deleterious results, so they suggest using transfection methods whereby the gene expression can be controlled (See Springer et al, Pg. 287, col. 1-2) or halting treatment after revascularization (See Rinsch et al, Pg. 524, col. 1). Following Springer et al's suggestion, it would have been obvious to one of ordinary skill in the art to use myoblasts which will transiently express the angiogenesis modulating gene(s); such methods were known in the art, see Penn et al.

Penn et al teach transfecting a population of skeletal myoblasts with a VEGF expression vector by plasmid DNA transfection (See Penn et al, Pg. 7, paragraph 0092). Penn et al also teach that the VEGF can be transiently expressed for any suitable and defined length of time (See Pg. 8, paragraph 0100-0102). Penn et al teach that local and transient expression of VEGF is sufficient to induce neovascularization and minimize systemic effects and hemangioma formation (See Penn et al, Pg. 1, paragraph 0004). With regards to the length of time the VEGF is produced, Penn et al teach that the duration of the transient expression is a result effective variable that would be routinely optimized by one of ordinary skill in the art (See Penn et al, pg. 8, paragraphs 0099-0102). Penn et al teach that the cells can be transiently transfected so as to express a therapeutic amount of VEGF; Penn et al further teaches that it is well within the scope of one skilled in the art to determine the appropriate therapeutic amount on an individual basis, as factors such as size, age, sex, presence of other drugs, and concentration of the active drug, all effect the optimal duration of expression. Therefore, the duration of the transient

expression of VEGF would have been routinely optimized by one of ordinary skill in the art at the time the invention was made, especially with lack of evidence to the contrary, submitting the claimed time period is critical. Penn et al further add that their cells, which transiently express VEGF, are useful to stimulate cell differentiation and regenerate ischemia damaged tissue (See Penn et al, Pg. 2, paragraph 0020 & Pg. 3, paragraphs 0044-0045). Therefore, at the time the invention was made, the benefits of transiently transfected cells, compared to constitutively transfected cells, was recognized in the art, and methods for producing such transiently transfected cells were known. Thus, in order to provide optimal and controlled delivery of the angiogenesis modulating agents, it would have been obvious to the artisan of ordinary skill to encapsulate transiently transfected cells in the methods of Springer et al and/or Rinsch et al. (relevant to claim 23).

Because the method of Naughton et al is intended to promote assimilation of the implanted tissue construct into the implantation tissue site, and to promote angiogenesis of the implanted tissue construct, as well as the ischemic tissue regions, and because the microencapsulated myoblasts of Springer et al and Rinsch et al are capable of promoting cell survival and angiogenesis, it is submitted that one of ordinary skill in the art would been motivated to co-implant the microencapsulated myoblasts of Springer et al and Rinsch et al, modified per the suggested method of Penn et al, for the purpose of enhancing cell survival and assimilation of the tissue construct of Naughton et al into the ischemic tissue site and to promote angiogenesis in and around the ischemic tissue site. One would have had a reasonable expectation of successfully co-implanting the encapsulated cells of Springer et al and/or Rinsch et al, modified to only transiently express the angiogenesis modulating agents, with the stromal tissue construct of Naughton et al because both Springer et al and Rinsch et al demonstrate that the microencapsulated cells can successfully be co-implanted at a target tissue site along with non-encapsulated cells, and the encapsulated cells do exert the predictable effect of enhancing cell survival and angiogenesis.

Thus, the cited references are considered to suggest a method of organ augmentation, specifically augmentation of the function of ischemic heart tissue, comprising: transiently transfecting a first population of cells (myoblasts) with a plasmid encoding the angiogenesis modulating agent VEGF, such that the myoblasts express the VEGF for less than about 3 weeks; encapsulating the transfected myoblasts (per the methods of Springer et al, Rinsch et al, and Penn et al); selecting a second population of cells, comprising myoblasts and vascular endothelial cells to be assimilated at the ischemic tissue region; culturing the second population of cells on an injectable polymer matrix to form a stromal tissue construct (per the method of Naughton et al); and co-implanting both the stromal tissue construct and the encapsulated myoblasts at the target ischemic region of the heart, thereby inducing assimilation and differentiation of the myoblasts and vascular endothelial cells into the ischemic tissue region, augmenting cardiac function.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 23-26, 28, 29, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (US 2003/0007954), in view of Atala (US Patent 6,479,064), MacLaughlin et al (US Patent 6,692,738), Springer et al (J Gene Med, 2000), Rinsch et al (Gene Therapy, 20001) and Penn et al (US 2004/0161412 A1, as fully supported by provisional applications 60/405274 & 60/424065).

The teachings of Naughton et al, Springer et al, Rinsch et al and Penn et al have been set forth above. The combined teachings are considered to render obvious the method of claims 23, 26, 28, 29, 36 and 37.

The combination of references differs from current claims 24 and 25 in that Naughton et al does not disclose use of a matrix comprising a hydrogel or decellularized tissue as the three-dimensional scaffold material for formation of the stromal tissue construct.

However, at the time the invention was made a variety of materials were recognized as suitable scaffolding materials for formation of engineered tissue constructs. Specifically, MacLaughlin et al disclose formation of tissue constructs using one of microfabricated scaffolds, fibrous scaffolds, or hydrogel matrices (See MacLaughlin et al, abstract). The fibrous scaffolds are identical to those disclosed by Naughton, being formed of polymers, such as polyglycolic acid and/or polylactic acid (See MacLaughlin et al, col. 13, ln 3-30). As an alternative, the hydrogel scaffolding material may be an injectable hydrogel material, such as alginate or hyaluronic acid (See MacLaughlin et al, col. 13, ln 42-col. 14, ln 35). Furthermore, Atala discloses various matrix materials and forms which are commonly used in the field of tissue engineering and cell delivery, including hydrogels and decellularized tissue (See, e.g. Atala, Pg. 1, paragraph 0012).

Therefore, because Naughton et al, MacLaughlin et al, and Atala all disclose scaffold materials which are appropriate for formation of engineered tissue constructs, it would have been *prima facie* obvious to one of ordinary skill in the art to substitute any of the scaffold materials for another, for the predictable result of successfully supporting growth of cells thereupon for formation of an engineered tissue construct which may subsequently be implanted at a target site. Substitution of one element for another known in the field is considered to be obvious, absent a showing that the result of the substitution yields more than predictable results. See *KSR International Co. v Teleflex Inc* 82 USPQ2d 1385 (US 2007) at page 1395. Therefore, substitution of polymer scaffolds comprising injectable hydrogels (disclosed by MacLaughlin et al & Atala) or decellularized tissues (disclosed by Atala) for the polymer scaffolding in the method of Naughton et al would have been *prima facie* obvious at the time the invention was made. (relevant to claims 24-26)

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Allison M. Ford/
Primary Examiner, Art Unit 1651